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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,423	04/05/2001	Jennifer L. Hillman	PF-0505-2-DIV	6586

27904 7590 06/17/2002

INCYTE GENOMICS, INC.
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EXAMINER	
DECLOUX, AMY M	

ART UNIT	PAPER NUMBER
1644	7

DATE MAILED: 06/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/828,423	Hillman et al.
Examiner	**Art Unit**
DeCloux, Amy	1644

-- The MAILING DATE of this communication appears on th cov r sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Mar 25, 2002

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-19 is/are pending in the applica

4a) Of the above, claim(s) 1, 2, 4, 7, 9, 10, 13, 18, and 19 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 3, 5, 6, 8, 11, 12, and 14-17 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on Apr 5, 2001 is/are a☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b) ☐ Some* c) ☐None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒Notice of References Cited (PTO-892)
2) ☐Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3
4) ☐Interview Summary (PTO-413) Paper No(s). _____
5) ☐Notice of Informal Patent Application (PTO-152)
6) ☐Other:

DETAILED ACTION

1. The Group and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Amy DeCloux, Group Art Unit 1644, Group 1640, Technology Center 1600.

2. Claims 1-19 are pending.

3. Applicant's election with traverse of Group II, (claims 3, 5-6, 8, 11-12 and 14-17) in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the invention encompassed by Group II could be examined at the same time as the inventions encompassed by the claims of Groups III-VIII because the searches would substantially overlap. This is not found persuasive because though there is some overlap in the searches of the distinct inventions, the searches are not co-extensive, and therefore an undue search burden would be placed on the examiner if the searches for Groups III-VIII were combined with Group II. However, in view of applicant's remarks, Group V (Claim 10) and Group VI (claim 13) will be rejoined with the claims of group II, upon their allowance.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 1-2, 4, 7, 9-10, 13 and 18-19 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

5. *35 U.S.C. § 101* reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, In such full, clear, concise, and exact terms as to enable any person skilled In the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 3, 5-6, 8 and 11-12 and 14-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility or a well-established utility.

The instant claims are drawn to an antibody to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, a biologically active fragment of the

amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of SEQ ID NO:1. The instant claims are not supported in the instant specification by either a specific and substantial asserted utility or a well-established utility. A well-established utility is a specific, substantial, and credible utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material.

The instant specification discloses on page 14, lines 18-19, that the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:1. The specification also discloses on page 14, lines 6-8, that the invention is based on the discovery of a new human growth associated protease inhibitor heavy chain precursor (GAPIP). However, the examiner notes that nowhere is it disclosed in the instant specification that SEQ ID NO:1 is GAPIP. Therefore technically there is no asserted utility for the polypeptide comprising SEQ ID NO:1, and no asserted utility for an antibody to SEQ ID NO:1. However, based on the context of the disclosure, for examination purposes SEQ ID NO:1 will be considered as being the amino acid sequence of GAPIP. (IE see page 14 of the instant specification) . APPLICANT IS REQUIRED TO CLARIFY.

The instant specification discloses on page 24 that GAPIP appears to play a role in reproductive, developmental, neoplastic and immunological disorders based on the expression of GAPIP in cancer, immune, reproductive, gastrointestinal, nervous and fetal tissues and based on its chemical and structural similarity among GAPIP and human pre-inter-a-trypsin inhibitor heavy chains. However it is noted by the examiner that it is not clear what type of molecule of GAPIP is being expressed, IE mRNA or protein.

However, without more guidance and direction from the instant specification, these disclosed asserted utilities of a protein comprising SEQ ID NO:1 are not credible nor well established for the following reasons. First, there is no disclosure that the protein of SEQ I NO:1 is actually translated since SEQ ID NO:1 appears to be deduced from a consensus nucleic acid sequence (SEQ ID NO:2) derived from overlapping and/or extended nucleic acid sequences (see page 14, lines 10-17). The presence of GAPIP RNA (if that is the case) does not necessarily mean that the protein is translated, as evidenced by Standart et al (Biochimie (1994) 76:867-879) who teaches translational regulation mediated by translational repressors that result in inhibition of translation initiation (see entire article, including the Abstract). It is also noted that there is no teaching in the prior art of a protein comprising SEQ ID NO:1, and the instant specification discloses only prophetic examples.

Further, the disclosed asserted utilities of GAPIP, which is for examination purposes being considered equivalent to the protein comprising SEQ ID NO:1, are based on GAPIP (nucleic or protein?) expression in a wide array of cell/tissue types with diverse functions, though there is no disclosure of a tissue that does not express GAPIP. It is noted that tissue specific

expression data by itself does not rely on specific properties or functions of the encoded protein, though evidence of a differential expression might serve as a basis for use of the claimed polypeptides. However, in the absence of any disclosed relationship between the claimed polypeptides and any function or any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696.

Furthermore, the asserted utility disclosed by the instant specification on page 25, lines 20-23, for an antibody which binds GAPIP is that the antibody may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express GAPIP, is neither a specific nor substantial asserted utility.

Therefore, the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility or a well-established utility. See also the Revised Interim Utility Guidelines available at www.uspto.gov.

7. Claims 3, 5-6, 8 and 11-12 and 14-17 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by a either a specific and substantial asserted utility, a credible asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. Claims 3, 5-6, 8 and 11-12 and 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

9. The instant claims are drawn to an antibody to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, a biologically active fragment of the amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of SEQ ID NO:1.

By reciting percent identity terminology in the instant claims, said isolated polypeptide can also encompass an indeterminate number and combination of amino acid substitutions in SEQ ID NO:1. However, applicants have not disclosed a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, nor an antibody to a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, other than SEQ ID NO:1 itself.

The term fragment is recited in the instant claims with open language of comprising. The instant specification discloses on page 7, lines 1-6, that an immunogenic fragment refers to

fragments of GAPIP which are preferably about 5-15 amino acids in length which retain some biological activity or immunological activity. Thus, by reciting the term fragment is recited in the instant claims with open language of comprising, the instant claims encompass an antibody directed to a polypeptide with an indeterminate number and sequence of amino acid residues in addition to only 5 consecutive residues of SEQ ID NO:1. Page 8 discloses that biologically active refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule, and discloses that immunologically active refers to the capability of GAPIP to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies. Given that the applicants have not disclosed a single fragment of the polypeptide comprising the amino acid sequence of SEQ ID NO:1, nor an antibody reactive with said fragment, and given that the instant specification does not provide compensatory structural or correlative teachings to enable one of skill to identify a polypeptide fragment of SEQ ID NO:1 with immunogenic or biological properties, encompassed by the method recited in said claims, one of skill would not be able to distinguish antibodies reactive to those fragments with said recited properties versus antibodies reactive to those fragments without said recited properties, without a further description from the instant specification. Therefore, the invention encompassing an antibody to said fragments is not adequately described.

The instant disclosure of an antibody to SEQ ID NO:1 does not adequately describe the scope of the claimed genus of an antibody to a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, a biologically active fragment of the amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of SEQ ID NO:1, which encompasses a substantial variety of subgenera. With the exception of an antibody to an isolated polypeptide molecule consisting of SEQ ID NO:1 itself, there is no description of the required structural features of said isolated polypeptide, nor of the conserved structural regions that would be critical for the disclosed utility of GAPIP. Without a description of the polypeptide, (with the exception of SEQ ID NO:1), there is not an adequate disclosed description of an antibody to a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, a biologically active fragment of the amino acid sequence of SEQ ID NO:1 or an immunogenic fragment of SEQ ID NO:1,

It is noted that though the claimed invention is directed to an antibodies to polypeptides and not cDNA, the principle of the following still holds for said antibodies: a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

The skilled artisan cannot envision all the contemplated antibodies and therefore

conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.)

10. Claims 3, 5-6, 8 and 11-12 and 14-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to an antibody to an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1, a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, a biologically active fragment of the amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of SEQ ID NO:1.

As discussed above in enablement rejection associated with the utility rejection of the instant claims, the instant specification provides insufficient guidance and direction regarding how to use the polypeptide comprising SEQ ID NO:1, and consequently there is also insufficient guidance and direction regarding how to use an antibody directed to the polypeptide comprising SEQ ID NO:1, a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, a biologically active fragment of the amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of SEQ ID NO:1 .

Furthermore the instant specification provides insufficient guidance and direction regarding how to make an antibody reactive with a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, a biologically active fragment of the amino acid sequence of SEQ ID NO:1 and an immunogenic fragment of SEQ ID NO:1 without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of antibodies, broadly encompassed by the claims.

By reciting percent identity terminology in the instant claims, said isolated polypeptide can also encompass an indeterminate number and combination of amino acid substitutions in SEQ ID NO:1. However, applicants have not disclosed a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, nor an

antibody to a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, other than SEQ ID NO:1 itself.

It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. As evidenced by Abaza et al (J. Of Protein Chemistry, 11(5):433-444) who teach that an amino acid substitution outside the antigenic site of a protein can exert drastic effects on the reactivity of a monoclonal antibody directed to the antigenic site, (see entire article, especially the abstract). The specification provides insufficient guidance as to the function of the instantly recited polypeptides. Without such guidance, such as guidance as to which 10% of the amino acids of SEQ ID NO:1 could be replaced by other amino acid residues, and still retain the function of a GAPIP protein is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without further guidance, making an antibody to a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The term fragment is recited in the instant claims with open language of comprising. The instant specification discloses on page 7, lines 1-6, that an immunogenic fragment refers to fragments of GAPIP which are preferably about 5-15 amino acids in length which retain some biological activity or immunological activity. Thus, by reciting the term fragment is recited in the instant claims with open language of comprising, the instant claims encompass an antibody directed to a polypeptide with an indeterminate number and sequence of amino acid residues in addition to only 5 consecutive residues of SEQ ID NO:1. Page 8 discloses that biologically active refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule, and discloses that immunologically active refers to the capability of GAPIP to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies. Given that the applicants have not disclosed a single fragment of the polypeptide comprising the amino acid sequence of SEQ ID NO:1, nor an antibody reactive with said fragment, and given that the instant specification does not provide compensatory structural or correlative teachings to enable one of skill to identify a polypeptide fragment of SEQ ID NO:1 with immunogenic or biological properties, encompassed by the method recited in said claims, one of skill would not be able to predict which fragments retain the recited properties, and thus one would not be able to know which fragments to use to make the recited antibody without further guidance and direction from the instant specification. Without further guidance, making an antibody to a naturally occurring amino acid sequence a biologically active fragment of the amino acid

sequence of SEQ ID NO:1 and an immunogenic fragment of SEQ ID NO:1, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

12. Claims 3, 5-6, 8 and 11-12 and 14-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 3, 5-6, 8 and 11-12 and 14-17 are indefinite because they depend on Claim 1 which is a non-elected claim .

B) Claims 3, 5-6, 8 and 11-12 and 14-17 are indefinite in the recitation "amino acid sequence of SEQ ID NO:1" because it is not clear if open or closed language is required. Inserting the term "consisting" or the term "comprising" would overcome the rejection.

13. An antibody directed to an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO:1 appears to be free of the prior art.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. a message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
Patent Examiner,
Art Unit 1644
Group 1640
June 17, 2002

Amy DeCloux
6-17-02